

Meeting Report

Agricultural Chemical Utilization and Human Health¹

by Elizabeth W. Mushak² and Warren T. Piver²

The public is justifiably concerned about the human health effects of agricultural chemicals. The many gaps in information about the mechanisms of toxic action, human exposures, and the nature and extent of human health effects are large. Very few older pesticides, in particular, have been tested for human health effects. Workers who produce, harvest, store, transport, process, and prepare food and fibers are exposed to many chemicals that are potentially hazardous and that are used in agriculture. The occupational health of these workers has not been adequately studied, and protective efforts have sometimes been minimal. Valid and accurate risk assessment is best based on sound information about how chemicals, in this case agricultural chemicals, are involved in toxic events—their mechanisms of action. These health effects include tumor promotion, chronic and acute neurotoxicity, immunotoxicity, and reproductive and developmental toxicity. Another key part of risk assessment is exposure assessment. Fundamental studies of the toxicology of target organisms and nontarget organisms exposed to agricultural chemicals are needed to discover and develop better solutions to the problems of agricultural pest control, including better formulations, optimal application rates and public education in safety and alternative agricultural practices. The large number of pesticides that have never been adequately tested for effects on human health is particularly worrisome in light of emerging information about delayed nervous system effects.

Introduction

Three to four percent of the United States' population produces virtually all the food and fiber for the nation and makes a significant positive contribution to the U.S. balance of trade. The producers and those who harvest, store, transport, and process the food and fiber may be at risk of adverse health effects from a variety of chemicals that contribute to American agricultural productivity. Speakers at this conference addressed human exposures to agricultural chemicals, basic research into the mechanisms of toxicity and biomarkers of exposure and effects, and prevention and treatment of human health effects.

The tone of the conference was set by acknowledging the complex nature of questions raised in the arena of agriculture and chemicals. Many classes of chemicals are put to many different uses and there can be no toxicity unless there is exposure. While some tests for exposure and for effects of exposure are available, laboratory tests are not necessarily the most appropriate way to determine what is occurring in fields, in granaries, in transit, and in food and fiber processing operations. Rather, it was suggested that research needs include an improved science base to reduce the uncertainties in risk assessment; the development of additional and new testing methods and new ways of using test data; and, science-based risk communication, done so well as to defuse public uncertainty.

Session I: Mode and Route of Human Exposure

Agenda

Robert Hollingworth, Michigan State University. Overview
George R. Hallberg, Iowa Department of Natural Resources.

Exposure to agricultural chemicals through drinking water
Christine F. Chaisson, Technical Assessment Systems, Inc.
Dietary exposure to agricultural chemicals and natural
toxics

Robert I. Krieger, California Department of Food And
Agriculture. Unintended and unavoidable pesticide ex-
posures in agricultural workplaces

Raymond S. H. Yang, National Institute of Environmental
Health Sciences. Assessment of health effects of pesti-
cide/fertilizer mixtures in contaminated groundwater: the
strategy and experimental approach

Roger F. Flattum, DuPont Agricultural Products. Trends in the
development and use of agricultural chemicals: an industry
viewpoint

Summary of Presentations

It is only within the last decade that credible evidence of a link between some agricultural chemicals and cancer has been established. Groundwater contamination from farm chemicals has occurred unrecognized for years and is now a potential source of exposure for those whose wells use water from contaminated aquifers. Concern about potential health effects of nitrates, the groundwater contaminant found at highest levels, is increasing, and the full dimensions of that and other contamination problems are unclear.

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Exposures to multiple chemicals represent difficult problems toxicologically, and no one has adequately addressed whether society is apportioning resources to answer the exposure and health effects questions commensurate with the potential risks. Alternatives to manufactured chemicals in agricultural practices must also be studied. Neither natural toxins in food plants nor the mechanisms of action of microbial pest controls have been adequately studied.

In the last 30 years, use of nitrates has increased 10-fold, and use of pesticides has increased by a factor of three to four. Over the same period, troubling data gaps in what happens to those chemicals have developed. The data gaps range from temporal and spatial disparities in sampling to seasonal differences in use and supply of contaminated groundwater. Many of the studies under way are using one sample, taken at one time of year, in one year.

The most commonly detected agrichemicals in groundwater are the volatile soil fumigants and nematicides used on vegetables and specialty crops, and the herbicides used on row crops. Some 35 to 40 agrichemical compounds have been found in groundwater in more than 30 agricultural states; adding samples of groundwater from areas of manufacturing and subsurface disposal sites raises the totals to 78 compounds in groundwater in 38 states.

Recent sampling of drinking water supplies indicates 35–40% of all Iowans use drinking water supplies with some detectable pesticide residues during the course of a year; 30–40% of the state's population uses drinking water supplies with half or more of Environmental Protection Agency (EPA) maximum contaminant level (10 mg/L) for nitrates. Some 130,000 rural Iowans are drinking from groundwater supplies with more than 10 mg/L (10 parts per million) nitrates. Iowa City is adding a \$3.5-million water treatment plant to remove nitrates and reduce drinking water nitrate levels below the EPA's standard, which is based on one in a million excess cancer risk.

Data gaps for drinking water contamination include the toxicological impact of the chemicals, methods to monitor the breakdown products of the chemicals, and their toxicological significance. One approach to evaluating potential risks of exposure to these chemicals is to look at the percentage of time chemical concentrations in drinking water sources exceed health advisory levels. For example, a 1989 U.S. Geological Survey sampling of triazine herbicide residues in 10 states of the upper cornbelt found 80% of water supplies contaminated in early (preherbicide treatment) spring, but contamination that was below the EPA advisory levels. After the herbicide was applied, 90% of surface supplies were contaminated, 55% above the EPA health advisory level (HAL) for atrazine and 34% above the HAL for alachlor.

An area that has received considerable attention is dietary exposure to agricultural chemicals and natural toxicants. Credible exposure assessment has been a weak link in risk assessment in the agricultural chemical setting for a long time. While monitoring agricultural products is currently in vogue, unless it is well done it becomes an abuse of private and public resources. The key problem is the focus on the raw products. To get products from the field to the dinner plate takes a number of steps, including extensive and sophisticated processing for many commodities, steps which may alter exposures for processors,

handlers, and ultimate consumers of the products in significant ways.

Dietary risk assessment attempts to determine concentrations of residues remain on or in food at the time the food is consumed. So far, aquaculture products are out of the EPA regulatory loop. Residues of agricultural chemicals, if any, are below the detection limit on some 80% of monitored samples. The Food and Drug Administration (FDA) database should focus on those areas with the greatest potential for residues if the sampling is properly designed.

The workplace is the place to look for human health effects from agricultural chemicals. Where scientists have rigorously measured exposures at different points in the manufacture and handling of pesticides and the harvesting of treated products, the exposures for harvesters are essentially equal to those for handlers who mix, load, and apply the chemicals. The difference between some harvesters and the mixer/handlers lies in the fact that the handler is in a more controlled setting. An analysis of where in the process from manufacture to use of pesticides excessive poisonings and excessive illnesses occur showed a rate of 1.44 per 10,000 for all agriculture, 50 per 10,000 for mixer/loaders, and 500 per 10,000 for grape pickers.

Differences were given for the extent of exposure for field workers by type of crop. For example, strawberry pickers are exposed to residues on plants from the elbow to the hand as they reach for the fruit; grape pickers experience whole body exposure to dislodgeable foliar pesticide residues because they use their whole bodies to expose, select, and pick the grapes throughout the grape harvest. It is difficult to explain to the public that such extended, intense harvesting exposures can be of real concern, while the product may be eaten with no health concerns at all, e.g., the food is safe to eat but not safe to pick.

The National Toxicology Program (NTP) has begun a program to assess the health effects of mixtures of pesticides and fertilizers in groundwater. Efforts were described to enhance the factual basis of formal risk assessment, now based primarily on single chemical exposures. The NTP project is designed to look at differences between binary and complex mixtures, using chemically defined mixtures related to patterns of groundwater contamination. The studies attempt to achieve environmentally realistic concentrations of chemicals and look at the potential for health effects from lifetime exposure. A "California mixture" and an "Iowa mixture" reflecting each state's use of agricultural chemicals are being studied in animals for several end points.

The kinds of toxicity seen with individual chemical exposures from the mixture include liver changes, immunosuppression, myelotoxicity, and cytogenetic changes. The questions are important when it is realized that more than one billion pounds of pesticides are used each year; some \$3 billion are invested in pest control to return \$12 billion in product. The public is directing questions about the safety of agricultural chemicals to scientists who have relatively few data to use to answer the questions. Future research should include pharmacokinetic modeling, application methods to increase target exposure and minimize environmental contamination, insect resistance, and cancer biology related to these exposures.

The production capacity for agricultural chemicals already exceeds demands and demand is dropping. Producers today evaluate about 50,000 compounds for each new one that reaches

the market, and spend roughly \$40–\$50 million to develop that one. The driving force for seeking new and safer products lies in demographics: the gap between world population growth and the amount of arable land is growing.

The large-scale production of pesticide chemicals began in the 1940s, and there are real opportunities for superior replacement products. The ideal pesticide would be benign except to its target, would tend not to move, and would tend to be gone by harvest. One such new type appears to be the sulfonylurea herbicides, which pose less of a threat than table salt, are applied at very low rates, and affect an enzyme found only in plants. Better application systems, packaging in either biodegradable or recyclable containers with formulations that eliminate dust or splashing, and the use of "on-target" application are among the changes now moving to market. At least as important, much more testing of toxic effects, identification of degradation products, and studies of transport in soils than was the case 3 years ago being done very early in new product development.

Session II: Mechanisms of Toxicity and Development and Use of Biomarkers

Agenda

Fumio Matsumura, University of California, Davis. Overview
James E. Trosko, Michigan State University. Modulated gap functional communication as a biomarker for multiple toxicities of pesticides

Janice E. Chambers, Mississippi State University. Mechanisms of acute neurotoxicity of insecticides

Vincent F. Garry, University of Minnesota. Chromosome rearrangements, pesticides and phosphine: pesticide applicators

Neil A. Chernoff, U. S. EPA. Test strategies for determination of potential reproduction and developmental toxicities: issues and limitations

Hanspeter Witschi, University of California, Davis. Pulmonary effects

James E. Riviere, North Carolina State University. Predicting dermal penetration and absorption of topically applied chemicals

Raghubir P. Sharma, Utah State University. Immunotoxic effects of agricultural chemicals

Summary of Presentations

The mechanism of action of organophosphates is a success story in scientific understanding of how a group of pesticides works. The compounds work by inhibiting cholinesterase, and there are known biomarkers of exposure, for example, acetylcholinesterase in blood and urinary metabolites of the compounds. Sodium channel activity, GABA receptor and dopamine receptor activity are targets of study by investigators seeking to understand how pyrethroids work. Major research areas for improving understanding of the activity of pesticides include mechanisms of cancer promotion; immunological effects; subtle and delayed neurotoxic effects including behavior, Parkinson's-like symptoms, and multiple sclerosis-like disease; lung toxicity; reproductive and developmental effects; nutrition and homeostasis; and biomarkers.

The potential utility of understanding communication among cells and disruption of the gap junctions that control those communications as keys in the mechanisms of action for assorted pesticides was described. The roles of the gap junction in inter-, intra-, and cell group cellular communications was outlined. Each of the levels of communication is subject to disruption with attendant consequences for normal cellular functioning, from altering homeostasis to blocking the signals for growth inhibition. Understanding how pesticides differentially affect cellular communication across the gap junctions could provide an explanation for the different toxicities that accompany different chemical exposures.

Using an interactive laser cytometer and appropriate markers, it is sometimes possible to identify where in the cellular communications networks some specific communications have been disrupted. The method appears to be useful for other than free-floating cells and may make it possible to define and better understand the mechanisms of action of many chemicals in the environment.

Older sources estimate that 500,000 pesticide poisonings occur around the globe each year. In many of the less developed countries, insecticides and acaricides are the most commonly used pesticides, and insecticides have a target organ that is common to both insects and vertebrates, the nervous system. The organochlorine insecticides, few of which are still approved for use in the United States, pose some special concerns for human health. This class of neurotoxic compounds was heavily used in the United States at one time, and the compounds tend to persist in the environment. The organochlorines include DDT, kepone, mirex, aldrin, dieldrin and chlordane, among others. While the pathways for some of these are well understood, they are less well defined for others.

The synthetic pyrethroids, which resemble the natural insecticide from chrysanthemums act via sodium channels much like the DDT group, but are generally readily detoxified and therefore have relatively low acute toxicity in mammals. Anticholinesterase insecticides like parathion act much like the World War II nerve gases and are quickly toxic. Carbamates, like Temik, can also operate through a different, noncholinesterase pathway, as do some of the organophosphorus (OP) insecticides. Both inhibit acetylcholinesterase, with the carbamates such as Sevin and Temik being relatively nonpersistent and the organophosphorus group such as Dursban being relatively persistent in the exposed organisms. Some of the OP insecticides also cause delayed permanent paralysis, an effect called organophosphate-induced delayed neuropathy (OPIDN).

Efforts to date to understand OPIDN have found that sensitivity and toxicity to these compounds is the reverse of expected: that is, the system is least sensitive to the most acutely toxic compound. In addition, there is still a question of what biochemical lesion is involved, and whether it may be the inhibition of neurotoxic esterase. Humans appear to be one of the most sensitive species to OPIDN.

One marker of exposure to the phosphine class of grain fumigants is increased unstable chromosome aberrations during the period when workers are applying these fumigants. Results were described that included time-related exposure differences, elevated numbers of chromosomal gaps and deletions, and studies showing delayed mitosis with very low exposures to

phosphine. Phosphine and other pesticide exposures appear to produce a chromosomal break pattern like that associated with non-Hodgkin's lymphoma. Alerting workers to measurable chromosomal changes reduced the incidence of such changes in subsequent seasons, probably because of better protective practices.

Reproductive and developmental toxicity concerns associated with pesticide use have evolved as a key end point for health effects research on pesticides. Multigenerational studies are now required for new pesticide registration, with information sought for effects of the compound on genetic integrity, gametogenesis, fertilization, implantation, embryogenesis, and fetal growth, maternal/neonatal relationship, and postnatal maturity. Increased accuracy in such assessments and better use of the existing database would improve test validity.

Problems of interpretation of such multigenerational studies persist, and there are neglected areas that may be productive for study. One of the intriguing findings that could be explored, for instance, was the incidence of anencephaly in offspring being related to the socioeconomic status of the mother as a child, not as an adult. Exploring the role of stress and nutrition could be a useful approach. The rapid expansion of information in biology and technology offers opportunities to improve the assays and the models being used.

The lung is one of the major pathways and targets of exposure to particles and gases, the ranging from mineral dusts like silica and plant dusts like cotton to the aerosols of pesticides and the gases and particulates in silos and animal confinement areas. Some of the exposures can kill lung cells, while others trigger proliferation of cells, leading to fibrosis. Some chemical forms are more hazardous to the lung than others, in particular the double-charged forms of quarternary nitrogen class, e.g., paraquat. Some agricultural chemicals are contaminated, and the contaminants are toxic in their own right. In addition, some agricultural practices, such as burning rice straw, may contribute to air pollution that has effects on the lung and moves beyond farm boundaries, as is occurring in the Central Valley of California.

The skin is both a major point of contact and route of entry for agricultural chemicals and an organ that actively metabolizes chemicals during absorption. The multiple roles of the skin were described, from barrier to transformation site, and the necessity was described for better understanding of the complexities of interaction between the skin and chemicals, in addition to the skin's function as a barrier. The monkey and the pig provide the best animal models for human skin. Good *in vitro* models of skin should incorporate the vasoactivity of the toxic compounds of interest as a factor in metabolism. An example of the information that can be missed in a simple, one-shot model is the amount of xenobiotic metabolized versus the amount taken in in a recirculating system. The single-pass measure shows 25% of the compound metabolized, whereas the percentage rises to 70% in a recirculating model exposure.

Examining the immunotoxic effects of exposure to agricultural chemicals is important because the immune system is a sensitive responder, serves in the body's defense system, is involved in hypersensitivity, and is part of the body's immune surveillance apparatus. The immune system responds both to synthetic and natural agricultural chemicals, from pesticides to aflatoxins. In addition to understanding the effects of agricultural chemicals on

immune competency, understanding the immune responses to exposure may lead to the development of useful biomarkers for exposures. Studies to date indicate that mycotoxins are more of a problem for immune responses than pesticides.

Session III: Human Health Effects and Prevention and Treatment

Agenda

James Marchant, University of Iowa College of Medicine. Overview

Aaron Blair, National Cancer Institute. Cancer epidemiology
Linda Rosenstock, University of Washington. Chronic neurological effects of organophosphate exposure

David S. Pratt, The Mary Imogene Bassett Hospital. Agricultural chemicals and the lung

Mary Wolff, Mount Sinai School of Medicine. Child health nutrition with reference to lactation

Lauren Zeise, California Department of Health Services. Risk assessment: perception and communication

Herbert B. Scher, ICI Americas. Formulation strategies for prevention

John E. Casida, University of California, Berkeley. Conference summary/analysis of future needs

Summary of Presentations

Prevention and treatment of the human health effects of exposure to agricultural chemicals has become more important with the development over the past 10 years of evidence for chronic sequelae as well as acute effects from exposure and the evidence of exposure for nonoccupational populations. In terms of occupational health and safety, exposure to agricultural chemicals is a global problem, not confined to the United States, with acute poisoning episodes far more common and severe in developing countries, where the likelihood of exposure to pesticides no longer registered in the United States is also greater.

Confining concern about agricultural chemicals only to agricultural interests has been succeeded in the United States by the widely held public perception that these chemicals are a public health problem, not just a problem for agriculture. As a result, the field is badly behind in all the disciplines that go into risk assessment. Resources for research are constantly being reduced. To illustrate the economic sector disparities in worker health and safety, agriculture spends 30 cents per worker on health and safety compared to \$180 per miner. Agricultural chemicals ranked at the top of farmer, farm family, and public concerns in an Iowa survey, despite the fact that deaths from farm injuries probably outpace deaths from agricultural chemical exposures by 40 to 1 (2000 versus 50).

The nature of the farm workforce was described as being both the single largest occupation in the country and a self-selected, quite healthy group to start with. Farming is an occupation requiring skills at management and many trades and encompassing many potential exposures, from solvents to exhausts as well as agricultural chemicals.

In looking for risks associated with farm exposures, elevated relative risk (compared to nonfarmers) for non-Hodgkin's lymphoma (NHL) has shown up for herbicide exposures, linked to

the number of days per year the farmer used pesticides and herbicides, and more specifically associated with the use of the herbicide 2,4-D. The elevated risk for NHL was not driven by use of insecticides. While several U.S. studies showed the risk elevation with herbicides, a Canadian study did not find an excess of cancer deaths associated with duration of use; however, relative risk increased with the number of acres sprayed in that study. Relative risk was also related to the dollars spent on fuel and oil, a surrogate for farm size. In a study of leukemias among Iowa and Minnesota farmers, a slight elevation of risk with pesticide use was found, and a greater risk was detected when the chemicals were used on animals than when they were used on crops, perhaps related to indoor use.

The largest percentage of accidental poisonings with agricultural chemicals occur with the organophosphate compounds in much of the world. There is reason for concern both because of the acute effects and the delayed effects of exposure to the compounds. An acute poisoning will produce a cholinergic crisis within hours; an intermediate episode may produce paralysis within days; delayed effects may appear as peripheral neuropathy within weeks; and some effects may linger for years. A recent World Health Organization (WHO) task force reported annual worldwide severe pesticide poisonings at 3,000,000, with 1,000,000 being occupational and the rest nonoccupational. Fatalities associated with the poisonings totaled 220,000, of which 20,000 were occupational. Studies using the WHO tests for cognitive response and processing of information showed performance decrements in exposed persons, and the results probably underestimate the chronic effects of high exposures, including subclinical poisonings. Studies to date have yielded inadequate evidence to relate chronic effects and exposure in the absence of overt toxicity, and much remains to be assessed and studied. However, exposure to organophosphates appears to be the best predictor of long-term neurological effects among workers exposed to neurotoxic pesticides.

The lung is the largest human surface exposed to the environment; smoothed out, the lung's surface would cover two tennis courts. Inhalation exposure to agricultural chemicals is one of the most common exposure paths and one with the potential for substantial health effects. For example, the common fertilizer ingredient ammonia causes alveolar damage when inhaled, and exposure to ammonia accounts for about one-third of farm work-related emergency room visits. The dipyrldyls like paraquat and Avenge, used to cause lower leaves to fall off of cotton, soybeans and sunflowers, produce peroxides and hydroxides which disrupt cells; giving oxygen to persons exposed to such dipyrldyls to help them breathe only makes the lung damage worse. Death after exposure to organophosphates usually is from respiratory collapse.

Other lung hazards come from the increasing use of livestock confinement operations, where hydrogen sulfide and methane can accumulate, and in crop storage areas where exposure to high levels of nitrogen oxides, ammonia, carbon dioxide, carbon monoxide, particulates, endotoxins, and mycotoxins can occur. The deaths of five persons were described at a livestock operation on the Upper Peninsula of Michigan in August of 1989. The first worker was overcome by gases from an unventilated, enclosed manure pit and fell in. Four others died in rescue attempts. The hazards of silo gases produced as plant nitrates degrade to nitrites and nitrous acid and the effects of exposure were described. The gases are poisonous to humans and livestock. The

danger period occurs within 10–12 hr of filling the silo with fresh material and continues for 10–14 days as the nitrates break down. For those exposed, the gases act like nitroglycerin, as a vasodilator, while the nitric acid damages alveoli in the lungs, with burnlike effects and edema. In these enclosed settings, understanding and communicating the risk means having workers use respirators to avoid the dangers.

The persistent nature of a number of environmental chemicals has been examined in studies of breastfeeding infants. Breastfeeding is encouraged for the benefits it offers the infant: appropriate amounts of energy for growth, nonallergenic α -lactoglobulin (versus cows' β -lactoglobulin), immune protection against diarrhea and respiratory infections, and a possible protective influence for later adult cholesterol levels and obesity control. One of the metabolites of DDT, DDE, is common in human breast milk and can hasten weaning because it acts like an estrogen to stop lactation. Phenobarbital, alcohol, and PCBs (polychlorinated biphenyls), pharmaceutical drugs, chemicals from smoking, lead, and a number of other heavy metals have been identified in human breast milk. While data on pharmaceuticals in breast milk is routinely available, such information is not available but is needed for pesticides and the lipid-soluble halogenated hydrocarbons. Much more information is needed on persistence and transfer in breast milk of the organophosphates and dichlorophenols as well.

Public perception of risk, whether from pesticides or other sources, is likely to be only as clear as the information the public has to consider, and is very much a function of the public's trust in the information source. Some of the practices and pitfalls were described that exist in assessing risk and communicating risk information, whether complete or not, to the public, and what incomplete information can do. When California found some watermelons with aldicarb on them, it created quite a stir. As in most such cases, the issues could be sorted as purely scientific; regulatory science; policy; and risk communication. The question of food safety came up again with Alar on apples, phrased as, "What's in the children's food?" Following a television program discussing potential cancer risk from cooked apple products, based on actual, but nongovernmental measurements of residues in products on the market, school boards took apples out of school cafeterias, and the message to the public about the safety of Alar was not clear at all.

A degradation product of Alar, UDMH (unsymmetrical dimethyl hydrazine), had been linked to cancer in experiments performed in 1967. Alar was registered as a pesticide in 1968. In 1972–1973, and again in 1977, independent studies showed a high incidence of two types of tumors in UDMH-exposed animals. In 1985, a science advisory panel to the U.S. Department of Agriculture under FIFRA (Federal Insecticide, Fungicide and Rodenticide Act) determined that existing studies did not provide enough information to do quantitative risk assessment for cancer from Alar. In 1987, EPA reduced allowable tolerances for residues of Alar on crops based on additional studies. In 1989, new studies with UDMH turned up the same kinds of tumors, hemangiosarcomas and lung tumors, as were found in the 1972–1973 and 1977 work. In 1989, EPA began the process of canceling registration of Alar.

Through all of this, there were few attempts to explain the FIFRA process to the public, and there was never a good explanation offered for what risk management is, how it is done,

and what it is meant to do. To communicate about risk, the communicator must be credible. Instead, as the questions piled up, EPA's responses sounded flippant, the manufacturer kept saying Alar was safe, and a Food and Drug Administration official appeared before a Congressional hearing where he twice kissed Meryl Steep (the spokesperson for the Natural Resources Defense Council, which brought the charges against Alar), and ate an apple. While the official handling of Alar may have been good science, it was bad public policy. In delaying action to get better data, regulators failed to use good scientific and public health judgment. The public forced a solution through the media and by way of political pressure, without waiting for the science.

Reducing the toxicity of pesticides to mammals and reducing the amount of pesticides that reach the environment are key goals of industry efforts to lessen the impact of pesticides. New forms and new packaging are designed to achieve both. Approaches include removing organic solvents from the formulations, substituting granules for liquids, using controlled release formulations, incorporating special surfactants to create a barrier at the water/skin border, and improving the distribution and application methods for pesticides. Most of these changes are nearing or in production and use modern techniques including microencapsulation and closed systems to meet the goals. Research and training is still needed, particularly in fundamental studies of physical and chemical interactions with substrates: soil, water, air, skin, plants, insects, and other ingredients of the commercial products.

The issues discussed in previous presentations were summarized and some suggestions were offered on future directions in research. To put the subject into perspective, there are 1200 registered pesticides, of which 900 are being produced and about 200 can be classified as major. Insecticides constitute 31% of the total, herbicides account for 24%, and fungicides 21%. Society's pressing needs are for better replacements that will be more selective in mode of action and target, safer to other than the target organisms, and more potent to reduce the environmental hazard by avoiding repeated applications. Among the probable sources for these replacements are natural products such as growth regulators and pheromones, parasitic organisms, and genetically engineered crops and pests, and synthetics based on rational or biochemical designs. As new classes of pesticides are identified to work on old targets, it is likely that new targets will also be found that will explain how the old pesticides worked. Thankfully there are a finite number of targets.

Recommendations

The organizers recommend substantial efforts and financial support for the following areas of research and training:

1. Human studies and epidemiology focusing on the occupationally exposed, with the goal of understanding their exposures, protecting them from adverse health effects, and identifying those aspects of agricultural chemical exposures that may be relevant to the general population. These studies would cover methods development, including new methods for exposure assessment, development and use of biomarkers of exposure, inquiry into the association between nitrate exposure and cancer, nitrate exposure and child development disorders, high-risk populations and their families, acute poisoning followups, and evaluation of toxic synergisms from exposure to mixtures.
2. More and better evaluation of the toxicity and human health effects of older pesticides, especially those not yet tested or evaluated for acute or chronic toxicity. Such testing and evaluation should address effects on organ function, perinatal toxicity, immunotoxicity, and chronic and delayed effects, including cancer and delayed nervous system manifestations.
3. Much better methods for identifying, quantifying, evaluating, and assessing human exposures for both occupationally exposed and environmentally exposed individuals and populations. Currently, no adequate database and methods exist for evaluating chronic and low-level exposures to any pesticide or the wide variety of agricultural chemicals that may be present in a given setting.
4. Studies to integrate accurate exposure assessment, adequate toxicological data, and adequate epidemiological data into quantitative risk assessment, and to develop new and better methods for science-based risk assessments.
5. Studies of the mechanisms of action of pesticides and other agricultural chemicals, synthetic and natural, in order to understand acute and chronic toxicity of the compounds and to provide avenues for the development of safer and more effective, more specific agricultural chemicals, as well as improving the practices for using existing and new chemicals.
6. Training of toxicologists, epidemiologists, and industrial hygienists in both agricultural chemicals and agricultural practices to support the development of better understanding of the interactions of humans and agricultural chemicals and better practices in the use of the chemicals.